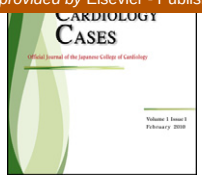
Journal of Cardiology Cases (2011) 3, e29–e32

journal homepage: www.elsevier.com/locate/jccase



Case Report

Multiple spontaneous coronary artery ruptures and cardiac tamponade in vascular Ehlers-Danlos syndrome

Yoshiaki Ohyama (MD)[a], Tatsuya Iso (MD, PhD)[a,b], Adriana Carolina Vargas Niño (MD)[a], Masaru Obokata (MD)[a], Rieko Takahashi (MD)[a], Wataru Okumura (MD, PhD)[a], Akihiko Nakano (MD)[a], Masao Amano (MD, PhD)[c], Isao Naito (MD, PhD)[d], Masamitsu Takatama (MD, PhD)[c], Masahiko Kurabayashi (MD, PhD, FJCC)[a,*]

[a] *Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan*
[b] *Education and Research Center, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan*
[c] *Department of Internal Medicine, Geriatrics Research Institute and Hospital, 3-26-8 Otomo-machi, Maebashi, Gunma 371-0847, Japan*
[d] *Department of Neurosurgery, Geriatrics Research Institute and Hospital, 3-26-8 Otomo-machi, Maebashi, Gunma 371-0847, Japan*

Received 1 August 2010; received in revised form 15 September 2010; accepted 24 September 2010

KEYWORDS
Ehlers-Danlos syndrome;
Carotid-cavernous fistula;
Coronary arterial rupture;
Cardiac tamponade;
Procollagen

Abstract We report a case of a 45-year-old woman with Ehlers-Danlos syndrome (EDS) type IV, the vascular type, who presented with multiple coronary artery ruptures causing cardiac tamponade. She had sudden onset of chest pain soon after transarterial embolization for right carotid-cavernous fistula. Transthoracic echocardiography confirmed cardiac tamponade and hypokinetic inferolateral wall. Enhanced CT and transesophageal echocardiography ruled out aortic dissection. Coronary angiography showed contrast extravasation from multiple sites of the right coronary artery and left circumflex coronary artery. We suspected EDS type IV, and a skin biopsy for DNA and RNA analysis was done after taking written informed consent. Polymerase chain reaction (PCR) and sequencing of the PCR product showed a heterozygous missense mutation of codon 85 in the *COL3A1* gene, which converted glycine to aspartic acid, and thus a diagnosis of EDS type IV was established. To our best knowledge, this is the first case of EDS type IV causing multiple coronary artery ruptures.

* Corresponding author. Tel.: +81 27 220 8140; fax: +81 27 220 8150.
E-mail address: mkuraba@med.gunma-u.ac.jp (M. Kurabayashi).

1878-5409/$ – see front matter © 2010 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.jccase.2010.09.002

Introduction

Spontaneous coronary artery rupture (SCAR) is a rare cause of cardiac tamponade and cardiogenic shock with a high mortality. Computed tomography (CT) is useful to rule out the aortic dissection which often causes cardiac tamponade. At coronary angiography, a definitive diagnosis of SCAR can be made by the observation of extravasation of contrast material anywhere in the coronary arteries. In contrast to naturally occurring coronary artery rupture, which happens in conjunction with blunt chest trauma, atherosclerotic disease, aneurysm, localized infection, and iatrogenic complications of percutaneous coronary intervention, SCAR may occur in patients with Ehlers-Danlos syndrome (EDS) type IV. EDS type IV, the vascular type, is a life-threatening autosomal dominantly inherited disorder of connective tissue, caused by mutation of the type III procollagen gene (*COL3A1*) [1]. EDS type IV causes severe fragility of connective tissues with arterial and intestinal ruptures. SCAR in patients with vascular EDS is rare, and there is only one case in the literature [2]. Furthermore, multiple SCARs associating with myocardial infarction have not been reported. We report here the first case of multiple SCARs complicating myocardial infarction in a 45-year-old female with EDS type IV.

Case

On May 25th in 2009, a 45-year-old woman was transferred to the emergency room from another hospital for suspected ST-segment elevation myocardial infarction (STEMI). She had sudden onset of chest pain soon after transarterial embolization for right carotid-cavernous fistula (CCF). Fifteen years before admission, she underwent transarterial embolization for left carotid-cavernous fistula (CCF). Since then, she had been regularly followed-up in out-patient clinic. On fourteen days before admission, she presented to the hospital with headache and tinnitus, and MRI revealed the right CCF. On May 25th, she underwent transarterial embolization for it. Although embolization was completed uneventfully, she developed chest pain in the recovery room when she became conscious after systemic anesthesia. ECG showed ST-segment elevation in II, III, aV_F, and V_4-V_6 leads suggesting acute myocardial infarction. Then, she was transferred to the catheter laboratory in our hospital. She had no classical risk factors for coronary artery disease. There was no family history of cardiovascular disease or sudden death.

On admission to our hospital, her blood pressure was 65/41 mmHg. Her pulse was 115/min and regular, and her body temperature was 36.3 °C. Arterial blood gas evaluation on O_2 2 l/min nasal showed pH 7.3; PaO_2 161.1 mmHg; $PaCo_2$ 23.7 mmHg; HCO_3^- 14.1 mmol/l; BE −9.4. She had a tendency of easy bruising, thin and translucent skin, atrophic scars of both knees, and hypermobility of metatarsophalangeal (MTP) joints of toes (data not shown).

An electrocardiogram (ECG) showed sinus tachycardia with ST-segment elevation in leads II, III, aV_F, and V_4—V_6 suggesting acute inferolateral (MI) (Fig. 1A). Total serum creatine kinase (CK) was 179 IU/l (reference range < 216 IU/l). Plasma troponin I was 4.71 ng/ml (reference range < 0.1 ng/ml). Transthoracic echocardiography confirmed cardiac tamponade and hypokinetic inferolateral wall. Computed tomography (CT) scanning with contrast agent (Fig. 1B) and transesophageal echocardiography ruled out aortic dissection. Stabilization was achieved with pericardiocentesis and blood transfusion. Surprisingly, coronary angiography (CAG) showed extravasation of contrast material from multiple sites in distal segments of the left circumflex artery (Fig. 2A) and right coronary artery (Fig. 2B). Vessels with ruptured sites were markedly spastic. Left ventriculography showed hypokinesis of inferolateral wall and no rupture of the ventricle.

Because blood oozing was barely detected by CAG performed at 30 min after the initial CAG, and because ECG showed that ST-segment almost returned to the baseline, we did not attempt to terminate bleeding at the ruptured sites. On the second hospital day, we confirmed no bleeding by CAG. The drain of pericardial cavity was removed uneventfully on the third day. Serum creatine kinase (CK) finally rose to a peak of 635 IU/l, and then returned to baseline within 3 days. The patient was discharged in good condition on the fifth day on calcium channel blocker and angiotensin-converting enzyme (ACE) inhibitor for secondary preventive medication.

Characteristic physical findings, thin and translucent skin, atrophic scars of both knees, and hypermobility (MTP) joints of toes, together with her clinical history of bilateral CCF, led us to the clinical diagnosis of vascular EDS. To confirm vascular EDS, a skin biopsy was performed. Informed consent was obtained from the patient for the DNA analysis before a skin biopsy.

To generate complementary DNA (cDNA), reverse transcription was performed using reverse transcription-polymerase chain reaction (RT-PCR) according to manufacturer's protocol. Sequencing of the PCR product including the 3.3 kb-pair of exons encoding the triple-helix domain of type III collagen was performed as previously described [3]. The results of the sequencing revealed a heterozygous missense mutation of codon 85 in the *COL3A1* gene, which converts codon GGT for glycine to codon GAT for aspartic acid (Fig. 3A, B and C), and thus a diagnosis of EDS type IV was established. To our best knowledge, this is the first case of EDS type IV causing multiple spontaneous coronary artery ruptures.

Discussion

The estimated prevalence of the EDS varies between 1/10,000 and 1/25,000 with no ethnic predisposition, and EDS type IV accounts for approximately 5—10% of all EDS [4]. The clinical diagnosis of EDS type IV is made based on the finding of at least two of four clinical criteria: easy bruising, thin skin with visible veins, characteristic facial appearance, and rupture of arteries, uterus, or intestines, but biochemical and molecular studies are required for confirmation [5]. The systemic arteries, which are rich in type III procollagen, may undergo dissection, aneurysm, or rupture. An arterial rupture may be preceded by either an aneurysm, arteriovenous fistula, or a dissection, but may also occur spontaneously. The *COL3A1* gene encodes 1467 amino acids, of which 1029 are located within the triple-helical domain

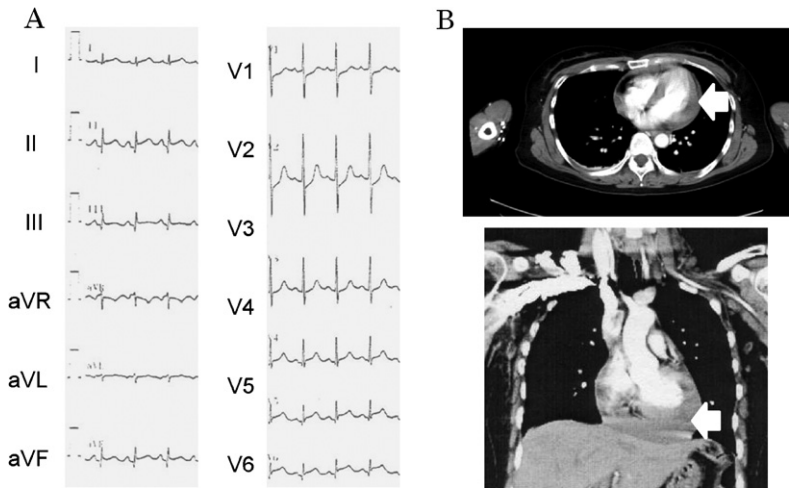


Figure 1 Electrocardiogram and enhanced CT images on admission. (A) On admission, ECG showed ST-segment elevated at II, III, aV_F, and V_4—V_6 leads. (B) Cross-section and frontal section of the heart showed massive pericardial effusion (arrow). There was no evidence of aortic dissection.

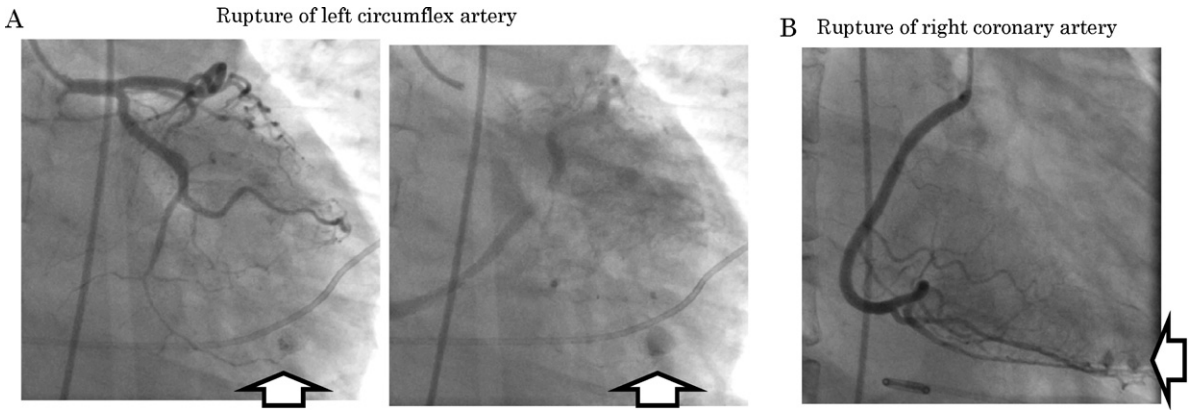


Figure 2 Emergent coronary angiography. Extravasation of contrast material (arrows) was detected at the distal segments of left circumflex artery (A) and right coronary artery (B). These segments were spastic.

consisting of the repetition of glycine-X-Y formation. The glycine is important for formation of the triple helix. Approximately two-thirds of published cases of EDS type IV with genetic analysis had the point mutations of glycine residues. The dissection or rupture site cannot be predicted and there seems to be no relation between location of the mutation in the *COL3A1* gene and the type of manifestations [1]. In our case, sequence analysis revealed a heterozygous missense mutation in the *COL3A1* gene, which converts the codon of GGT for glycine at amino acid position 85 to the codon of GAT for aspartic acid. This mutation has been reported but no detailed information about clinical manifestation was available [1].

Arterial rupture is a leading cause of death in the patients with EDS type IV [1]. Among arterial ruptures and dissection that have been documented so far in the patients with EDS type IV, spontaneous coronary artery dissection (SCAD) or SCAR are very rare compared with the dissection and rupture in other arteries such as aorta, renal, hepatic, and iliac arteries [6—9]. Indeed, there has been only one case report of SCAR [2], and there have been no case reports of multiple SCAR. Thus, this is the first report of multiple SCARs confirmed by CAG. As is often the case with catastrophic disorders, SCAR might be underreported because an acute bleeding in the pericardium is often lethal and thus likely to be recognized. In addition, pre- or postoperative CAG failed to show local coronary pathology in most cases [10].

The trigger of multiple coronary artery ruptures remains speculative. Our patient underwent transarterial embolization for CCF via the femoral artery and the femoral vein before this admission. Given that our patient presented with acute MI, and CAG revealed the spastic coronary arteries, the most likely explanation would be that intraoperative emotional and hemodynamic stress may have caused vasospasms of multiple sites of coronary arteries, and the vasospasm may have induced tear of the friable arterial walls.

In conclusion, we report the first case of multiple SCARs with EDS type IV, in which acute MI and cardiac tamponade developed. When encountered with multiple ruptures of

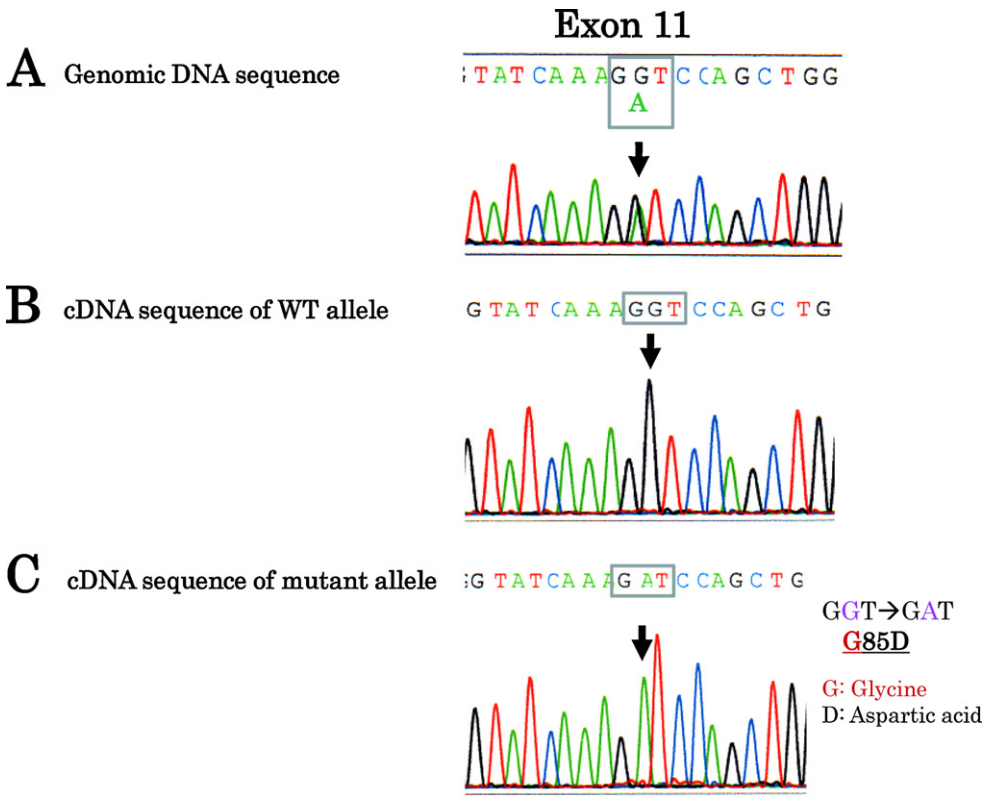


Figure 3 Missense mutation of codon 85 in the *COL3A1* gene. (A) Genomic DNA sequence of exon 11 in the patient DNA isolated from peripheral blood. G and A residues are found at the same position (arrow), indicating the different sequence of the two alleles. cDNA sequence of wild type allele (B) and mutant allele (C). Arrows indicate the substituted bases. Mutation from GGT to GAT causes substitution of aspartic acid for glycine in the glycine-X-Y repeats in the triple-helix region of the *COLl3A1* gene.

coronary arteries, cardiologists and emergency care physicians should pay attention to vascular fragility and suspect EDS type IV.

References

[1] Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N Engl J Med 2000;342:673—80.
[2] Evans RH, Fraser AG. Spontaneous coronary artery rupture and cardiac tamponade in Ehlers-Danlos syndrome type IV. Int J Cardiol 1996;54:283—6.
[3] Tromp G, Wu Y, Prockop DJ, Madhatheri SL, Kleinert C, Earley JJ, et al. Sequencing of cDNA from 50 unrelated patients reveals that mutations in the triple-helical domain of type III procollagen are an infrequent cause of aortic aneurysms. J Clin Invest 1993;91:2539—45.
[4] Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, et al. International nosology of heritable disorders of connective tissue, Berlin, 1986. Am J Med Genet 1988;29:581—94.
[5] Beighton P, De Paepe A, Hall JG, Hollister DW, Pope FM, Pyeritz RE, et al. Molecular nosology of heritable disorders of connective tissue. Am J Med Genet 1992;42:431—48.
[6] Wan S, LeClerc JL, Vachiery JL, Vincent JL. Cardiac tamponade due to spontaneous rupture of right coronary artery aneurysm. Ann Thorac Surg 1996;62:575—6.
[7] Badmanaban B, McCarty D, Mole DJ, McKeown PP, Sarsam MA. Spontaneous coronary artery dissection presenting as cardiac tamponade. Ann Thorac Surg 2002;73:1324—6.
[8] Oderich GS, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. J Vasc Surg 2005;42:98—106.
[9] Nakamura M, Yajima J, Oikawa Y, Ogasawara K, Uejima T, Abe K, et al. Vascular Ehlers-Danlos syndrome—all three coronary artery spontaneous dissections. J Cardiol 2009;53:458—62.
[10] Nishiyama Y, Nejima J, Watanabe A, Kotani E, Sakai N, Hatamochi A, et al. Ehlers-Danlos syndrome type IV with a unique point mutation in COL3A1 and familial phenotype of myocardial infarction without organic coronary stenosis. J Intern Med 2001;249:103—8.